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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/527,411 | SHONE ET AL. | |
| | Examiner | Art Unit | |
| | Nina A. Archie | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***DETAILED ACTION***

1. This Office Action is responsive to Applicant's amendment and response filed 2-1-10. Claims 1-30 are pending and under examination. Claims 1-3, 5, 7, 9-11 have been amended.

2. The declaration under 37 CFR 1.132 filed 2/1/2010 and signed by Clifford Shone and dated 11/23/2009 is considered.

***Objections/Rejections Withdrawn***

3. In view of the Applicant's amendments and remarks the following objections/rejections are withdrawn.

a) Objection to claim 18 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of independent claim 1 is withdrawn in light of applicant's amendment thereto.

b) Objection to the specification for the disclosure of the following informalities: p. 3, Kozaki et al citation is incomplete 1 is withdrawn in light of applicant's amendment to specification filed 2/1/2010.

c) Rejection to claims 1-30 under 35 U.S.C. 102(b) as being anticipated by Binz et al 1990 J. Biological Chemistry. Vol. 265 No. 16 1990 pgs. 9153-9158 is withdrawn in light of applicant's amendment thereto, applicant's argument, and the limitation of lacking a functional C-terminal part of a clostridial neurotoxin heave chain.

d) Rejection to claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14, 16-32, 34, 37-39, and 54 of copending US Application No. 11/644,010 **is withdrawn in light of the application is presently abandoned on 10/28/2009.**

e) Rejection to claims 1-3, 5-15, and 17-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 11-23, 25-26 of copending US Application No. 11/077,550 **is withdrawn in light of instant application presently granted US Patent No. 7674470 B2 (see rejection below).**

f) Rejection of claim 1 as being vague and indefinite in the recitation of "capable of' under 35 U.S.C. 112, second paragraph, is withdrawn in light of applicant's amendment thereto.

g) Rejection of claims 1 and 5, reciting the phrase "portion" under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of applicant's amendment thereto.

h) Rejection of claims 2-3, 5, and 14, reciting the limitation "clostridial toxin heavy chain" as is insufficient antecedent basis for this limitation in the claims under 35 U.S.C. 112, second paragraph is withdrawn in light of applicant's amendment thereto.

i) Rejection to claims 1-18, 24, and 26-30 rejected under 35 U.S.C. 102(e) as being anticipated by Shone et al. US Patent No. 7,192596 Date March 20, 2007 US Filing Date September 12, 2002 is withdrawn in light of applicant's amendment thereto.

j) Rejection to claims 1-3, 5-15, and 17-18 rejected under 35 U.S.C. 102(e) as being anticipated by Shone et al. US Application 20050244435 US Publication and Filing Date March 11, 2005 is withdrawn in light of applicant's amendment thereto.

### *Claim Rejections Maintained*

#### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ormum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. The rejection of claims 1-18, and 24, 26-30 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10-17, 20-29, 31, and 39-42 of US Patent No. 7,192596 are maintained for the reasons set forth previous office action.

Examiner notes that Applicants state the rejection are held in abeyance until the claimed subject matter is otherwise deemed allowable. Applicants will consider filing a terminal disclaimer if necessary to overcome any obviousness-type double patenting.

As outlined previously, claims 1-18 and 24, 26-30 of in the instant application are drawn to an isolated polypeptide, wherein said isolated polypeptide is a single chain polypeptide selected from the group consisting of: (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (II) a fragment of the single chain polypeptide (I) that is at least 80% the length thereof, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or fragment thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis, and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a fragment thereof that (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (III) a variant of the single chain polypeptide of (I) having at least 80% amino acid sequence homology therewith, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or a variant thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to excocytosis and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a variant thereof that (i) translocates the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its

own; and wherein said variant of the single chain polypeptide lacks a function C-terminal part of a clostridial neurotoxin heavy chain $H_C$, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (claim 1), wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain (claim 2), wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain (claim 3), wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin (claim 4), wherein said second domain is a clostridial toxin heavy chain HN portion (claim 5), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (claim 6), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (claim 8), wherein the second domain comprises the 107 N-terminal or 423 N-terminal amino acids of a botulinum neurotoxin type A and B heavy chains (claims 7 and 9), wherein the second domain comprises the 417 N-terminal amino acids of botulinum neurotoxin type B heavy chain (claim 10), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (claim 11), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (claim 12), comprising a site for cleavage by a proteolytic enzyme (claim 13), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 14), wherein the cleavage site allows proteolytic cleavage of the first and second domains (claim 15), wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein that does the polypeptide prior to said proteolytic cleavage (claim 16), a polypeptide obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide (claim 17), wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc (claim 18), including a spacer molecule between the first and second domains (claim 24), comprising a site for cleavage by a proteolytic enzyme (see claim 26), including a spacer molecule between the purification tag and the polypeptide (claim 27), wherein said purification tag binds to an affinity matrix of glutathione sepharose (claim 28), wherein first protease cleavage site is incorporated between said single chain polypeptide and the purification tag said protease cleavage site enabling proteolytic separation of said polypeptide from said

purification tag (claim 29), wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains (claim 30).

B) Claims 1-8, 10-17, 20-29, 31, and 39-42 of US Patent No. 7,192596 teach a single chain polypeptide selected from the group consisting of: (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 1), wherein said clostridial neurotoxin light chain is a botulinum neurotoxin light chain (see claim 2), wherein said clostridial neurotoxin light chain is a tetanus neurotoxin light chain (see claim 3), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin heavy chain (see claim 4), wherein said clostridial neurotoxin heavy chain is a tetanus neurotoxin heavy chain (see claim 5), wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin (see claim 6), wherein said second domain is a clostridial neurotoxin heavy chain HN portion (see claim 7), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (see claim 8), wherein the second domain comprises the 423 N-terminal amino acids of botulinum neurotoxin type A heavy chain (see claim 10), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (see claim 11), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum neurotoxin type B heavy chain (see claim 12), wherein the second domain comprises the 417 N-terminal amino acids of botulinum neurotoxin type B heavy chain (see claim 13), wherein the clostridial neurotoxin light chain is a botulinum neurotoxin type B light chain, and the second domain comprises the 417 N-terminal amino acids of a botulinum neurotoxin type B heavy chain (see claim 14), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a tetanus toxin chain (see claim 15), wherein the second domain comprises the 422 N-terminal amino acids of tetanus

heavy chain (see claim 16), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (see claim 17), comprising a site for cleavage by a proteolytic enzyme, wherein said cleavage site is located between said first domain and said second domain ( see claim 20), wherein the cleavage site is not present in a native clostridial neurotoxin ( see claim 21), wherein the site for cleavage allows proteolytic cleavage of the first and second domains ( see claim 22), wherein the site for cleavage allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein than does the polypeptide prior to said proteolytic cleavage ( see claim 23).

US Patent No. 7,192596 teach a polypeptide produced by a process comprising (a) inserting a first nucleic acid sequence encoding said cleavage site into a second nucleic acid sequence encoding the polypeptide, and (b) expressing said first and second nucleic acid sequences to obtain said polypeptide (see claim 24); a fusion protein consisting essentially of a fusion of (a) a single chain polypeptide consisting essentially of first and second domains and (b) a purification tag that binds to an affinity matrix thereby facilitating purification of the fusion protein using said matrix (see also claim 41); wherein said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein the second domain lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated HC thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 25), wherein said purification tag binds to an affinity matrix of glutathione sepharose (see claim 26), wherein a first protease cleavage site is incorporated between the polypeptide and purification tag said first protease cleavage site enabling proteolytic separation of the polypeptide from the purification tag (see claim 27), including a spacer molecule between the purification tag and the polypeptide (see

claim 29); a single chain polypeptide consisting of first and second domains, wherein: said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein the second domain lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated HC thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 31), wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains (see claims 39-40), further comprising a spacer molecule between the first and second domains (see claims 28 and 42), wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein that does the polypeptide prior to said proteolytic cleavage (see claim 23), wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains (see claim 25).

Although the conflicting claims are not identical, they are not patentably distinct. The U.S. Patent No. 7,192596 recites the "single chain polypeptide". The species of the "single chain polypeptide" anticipate the genus claims of any "single chain polypeptide".

Thus, claims 1-18, and 24-30 encompassing the "the isolated polypeptide" in the present application are obvious over claims 1-8, 10-17, 20-29, 31, and 39-42 of US Patent No. 7,192596.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***35 USC § 112***

***Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The claims are drawn to an isolated polypeptide, wherein said isolated polypeptide is a single chain polypeptide selected from the group consisting of: (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (II) a fragment of the single chain polypeptide (I) that is at least 80% the length thereof, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or fragment thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis, and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a fragment thereof that (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (III) a variant of the single chain polypeptide of (I) having at least 80% amino acid sequence homology therewith, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or a variant thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to excocytosis and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a

variant thereof that (i) translocates the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said variant of the single chain polypeptide lacks a function C-terminal part of a clostridial neurotoxin heavy chain $H_C$, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (claim 1), wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain (claim 2), wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain (claim 3), wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin (claim 4), wherein said second domain is a clostridial toxin heavy chain HN portion (claim 5), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (claim 6), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (claim 8), wherein the second domain comprises the 107 N-terminal or 423 N-terminal amino acids of a botulinum neurotoxin type A and B heavy chains (claims 7 and 9), wherein the second domain comprises the 417 N-terminal amino acids of botulinum neurotoxin type B heavy chain (claim 10), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (claim 11), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (claim 12), comprising a site for cleavage by a proteolytic enzyme (claim 13), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 14), wherein the cleavage site allows proteolytic cleavage of the first and second domains (claim 15), wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein that does the polypeptide prior to said proteolytic cleavage (claim 16), a polypeptide obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide (claim 17), wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc (claim 18), further comprising a third domain that binds the polypeptide to a cell, by binding of the third domain directly to a cell or by binding of the third domain to a ligand

or to ligands that bind to a cell (claim 19), wherein said third domain is for binding the polypeptide to an immunoglobulin (claim 20), wherein said third domain is a tandem repeat synthetic IgG binding domain derived from domain b of Staphylococcal protein A (claim 21), wherein said third domain comprises an amino acid sequence that binds to a cell surface receptor (claim 22), wherein said third domain is insulin-like growth factor- 1 (IGF- 1) (claim 23), including a spacer molecule between the first and second domains (claim 24), including a spacer molecule between the second and third domain (claim 25), further comprises a purification tag that binds to an affinity matrix thereby facilitating purification of the polypeptide using said matrix (claim 26), including a spacer molecule between the purification tag and the polypeptide (claim 27), wherein said purification tag binds to an affinity matrix of glutathione sepharose (claim 28), wherein first protease cleavage site is incorporated between said single chain polypeptide and the purification tag said protease cleavage site enabling proteolytic separation of said polypeptide from said purification tag (claim 29), wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains (claim 30).

The rejection of claims 1-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description rejection.

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph on February 1, 2010 is carefully considered, but not found to be persuasive for the reasons below.

**Applicant argues**:

(A) Applicants assert that the present specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing the application. Applicant argues the as-filed specification provides as disclosed on pages 5-8, the structure of clostridial neurotoxins and the function of

their light chain and HN domains was well-known prior to the filing of the present application. For example, Kurazano, H., et al., J. Biol. Chem. 267:14721-14729 (hereinafter "Kurazano") (cited on page 5 of the as-filed specification, attached herewith as Exhibit A), discloses the minimum domains necessary for cleavage activity (e.g. proteolytic enzyme activity) of a clostridial neurotoxin L-chain. The as- filed specification states that: Table II on page 14726 of Kurazano et al. (1992) illustrates a number of L-chain deletion mutants (both amino-terminal and carboxy-terminal L- chain deletion mutants are illustrated). Such mutants, together with other L-chain mutants containing, for example, similar amino acid deletions or conservative amino acid substitutions are embraced by the first domain definition of the present invention provided that the L-chain component in question has the requisite cleavage activity (see page 5, lines 7-12 of the as-filed specification). Kurazano also discloses the structure of clostridial neurotoxin heavy chains, together with the functions associated with the HN domain of the heavy chain (see Figure 1 on page 14722 of Kurazano).

(B) The as-filed specification discloses that the sole requirement for a fragment or variant of the first domain is that it retains the cleavage function of a clostridial neurotoxin light chain (page 4, lines 27-28). The as-filed specification further discloses that a fragment of the first domain can be a "N-terminal, C-terminal fragment of the light chain, or is an internal fragment, so long as it substantially retains the ability to cleave the vesicle or plasma-membrane associated protein essential to exocytosis" (page 12, lines 20-22). The as-filed specification also discloses that the variant of the first domain "has a different peptide sequence from the light chain or from the fragment, though it too is capable of cleaving the vesicle or plasma-membrane associated protein" (page 12, lines 23-24). The variant may differ from the reference sequence by way of one or more amino acid insertions, deletions, and/or substitutions. In some embodiments, the variant sequence may comprise an N-terminal extension, a C-terminal extension, and/or one or more amino acid alterations as compared to the sequence of a clostridial neurotoxin light chain (page 12, line 27, through page 13, line 3).

(C) The as-filed specification discloses that the sole requirement for a fragment or variant of the second domain is that it retains the translocation and/or solubilizing activity of a clostridial neurotoxin heavy chain HN (page 6, lines 23-25). The as-filed specification discloses that simple assays were available before the filing date of the application to determine whether a particular

clostridial neurotoxin HN portion (or equivalent HN component) had the requisite translocation function (page 7, lines 5-7). The as-filed specification further provides written description for the fragments and variants of the second domain which are "conveniently obtained by insertion, deletion and/or substitution of a HN domain or fragment thereof' (see page 13, lines 13-25).

(D) The as-filed specification further discloses that prior to the present application a number of conventional, simple assays were available to allow a skilled person to routinely confirm whether a given L-chain (or equivalent L-chain component) had the requisite cleavage activity. These assays are based on the inherent ability of a functional L-chain to effect peptide cleavage of specific vesicle or plasma membrane associated proteins (eg. synaptobrevin, syntaxin, or SNAP-25) involved in neuronal exocytosis, and simply test for the presence of the cleaved product/s of said proteolytic reaction (see page 5, lines 13-19). Conventional assays suitable for detecting clostridial neurotoxin HN polypeptide translocation activity are described in Blaustein, R.O., et al, FEBS 226: 115-120 (1987)(attached herewith as Exhibit B) and Shone, C.C., et al., Eur. J. Biochem. 167:175-180 (1987)(attached herewith as Exhibit C).

(E) The as-filed specification also discloses the preparation of the variant single- chain polypeptides shown in SEQ ID NOs: 2, 4, 10, 12, and 26 (see Example 1, pages 62-68) and SEQ ID NOs: 20, 22, and 24 (Example, 2, pages 68-69). These variants comprise multiple amino acid substitutions and/or insertions/extensions as compared with the amino acid sequence of the corresponding clostridial neurotoxin light chain and heavy chain HN. Additionally, the expression of a variant single-chain polypeptide in E. coli is disclosed in Examples 4-9 of the as-filed specification (pages 71-75). These single-chain variant and fragment polypeptides contain deletions in the second domain as compared to the corresponding clostridial neurotoxin heavy chain HN.

(F) Although the Applicant could have disclosed additional representative members of the genus of single chain polypeptides, it was not necessary to do so, because it is not necessary to disclose what was already known in the art. Support for this conclusion is found in Invitrogen Corporation v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005), in which the independent claim at issue recited "[a]n isolated polypeptide having polymerase activity and substantially reduced RNase H activity" Id. at 1072. In Invitrogen, Clontech argued that Invitrogen's claims were invalid for lack of written description, because the claims were "not

limited to sequences recited in the specification and do not recite DNA or protein sequences." Id. at 1073. The Federal Circuit rejected Clontech's argument, and explained that "the district court found it undisputed that in addition to the sequence recited in the specification at bar, 'at the time of the invention, the sequences of RT genes were known and members of the RT gene family shared significant homologies from one species of RT to another.'" Id. (quoting Invitrogen Corp. v. Clontech Labs., Nos. AW-96-4080, AW-00-1879 (D.Md. October 17, 2003)). The Federal Circuit also rejected Clontech's argument that University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Circ. 1997), compelled a conclusion that Invitrogen's claims were not described. See id. The Federal Circuit affirmed the district court's holding that Invitrogen's claims were not invalid for lack of written description. See id. at 1073-74. Thus, under Invitrogen, it was not necessary to provide an exhaustive list of representative members in the present specification in order for the single chain polypeptide to be described, because, as discussed above, many representative members of the genus of single chain polypeptides were known in the art.

**Examiner's Response to Applicants arguments**:

With regard to Points (A) and (B), the independent claim is drawn to an isolated polypeptide encompassing a single chain polypeptide comprising (I) SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (II) a fragment of the single chain polypeptide (I) that is at least 80% the length thereof; or III) a variant of the single chain polypeptide of (I) having at least 80% amino acid sequence homology therewith, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or fragment thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis, and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a fragment thereof that (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and

increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

Moreover, the specification discloses fragments and or variants regarding cleavage (see p. 4; see also pp. 12-13), translocation, and solubility activity (see pgs. 6-7; see also p. 13). The specification discloses $LH_N$/A incorporating an enterokinase protease activation site at the LC-$H_N$ junction and a C-terminal $(Glu)_8$ peptide (see pg. 44). The specification discloses SEQ ID NO: 24 a botulinum $H_N$ polypeptide fragment having only 107 residues sufficient to maintain solubility of a single chain polypeptide known as ($LH_{107}$/B, SEQ ID NO: 24) (see Example 2) which does not suggests that the specification discloses a core structure of the instant claims because the claimed invention is drawn to SEQ ID NO: 66. Furthermore, the core structure is not well known in the art, therefore one skilled in the art would not know the functions of any fragments or variants associated with the domains of the heavy and light chain domains of clostridial neurotoxins. Therefore the descriptions of fragments and variants of clostridial neurotoxins in the specification that Applicants stated in their response aforementioned above is merely representative of the claimed invention.

The specification is only limited to (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. **Therefore SEQ ID NO: 66 meet the written description requirement not fragment or any variants of the claimed invention.**

The specification does not provide adequate description of the claimed genus of variants in (II) or (III) aforementioned above. Applicants have not disclosed in the specification any such fragment or variant of at least 80% sequence identity to SEQ ID NO: 66 that must retain the "cleavage", translocation, and/or improved solubility function. Moreover, Applicant has not

specifically demonstrated in of at least 80% SEQ ID NO: 66 which C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ conveys the ability of thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds is indicated as not functional. Applicant has not specifically disclosed the structure of a fragment or variant of at least 80% sequence identity to the single chain polypeptide of SEQ ID NO: 66 that encompasses said first and second domains set forth supra capable of the recited functions. Applicants has not specifically disclosed the structure or fragment in the first domain of the fragment or variant thereof of at least 80% sequence identity to SEQ ID NO: 66 that must be retained to posses the abilities to cleave one or more vesicle or plasma membrane associated proteins essential to exocytosis, and the structure or fragment in the second domain the fragment or variant thereof of at least 80% sequence identity to SEQ ID NO: 66 that must be retained to posses the abilities to (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. Therefore in regards to Applicants response the structure of clostridial neurotoxins and the function of their light chain and HN domains as being well-known at the time of filing is unpersuasive.

Moreover, the reference Kurazano, H., et al., J. Biol. Chem. 267:14721-14729 cited by Applicant, disclosing the minimum domains necessary for cleavage activity and the structure of clostridial neurotoxin heavy chains, together with the functions associated with the HN domain of the heavy chain is also unpersuasive. Kurazano, H., et al., J. Biol. Chem. 267:14721-14729 does not indicate the domains necessary for cleavage activity, Kurazano et al only states the minimum domains necessary for cleavage activity or indicative of specific fragments within the heavy chain that retains the functional limitation of cleavage activity. Therefore one skilled in the art would not accept on its face the examples given in the specification nor the reference of

Kurazano et al aforementioned above cited by applicant as being correlative or representative of a successful model for the claimed invention.

With regard to Points (C) and (D), the specification does not provide a core structure of SEQ ID NO: 66 which correlates to the recited function. Moreover, said core structure was not known in the art. Consequently one skilled in the art would not know the functions of any fragments or variants associated with the domains of the heavy and light chain domains of clostridial neurotoxins. The specification does not adequately describe at least a substantial number of members of the genus variants or fragment in (II) and (III) aforementioned above to which the claims are based. Therefore, one skilled in the art would not be able determine whether a particular clostridial neurotoxin HN portion (or equivalent HN component) had the requisite translocation function and translocation activity as described (attached herewith as Exhibits B and C) in any simple assay because SEQ ID NO: 66 is not well known in the art and Applicants have not demonstrated that any fragment or variant is representative of the recited functions. Moreover, the presence or absence of an assay is not germane as written description requires possession of an invention not a means of isolating it. Furthermore, the specification does not disclose the sole requirement for a fragment or variant of the second domain so that it retains the translocation and/or solubilizing activity of a clostridial neurotoxin heavy chain HN (page 6, lines 23-25) therefore one skilled in the art would not know the sole requirement aforementioned above because SEQ ID NO: 66 is not well known in the art. Moreover, Applicants have not demonstrated in at least 80% sequence identity to SEQ ID NO: 66 which C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ conveys the ability of rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds is indicated as not functional. Applicants have not specifically disclosed the structure of a fragment or variant of at least 80% sequence identity of the single chain polypeptide of SEQ ID NO: 66 that encompasses said first and second domains set forth supra capable of the recited functions. Furthermore, applicants also have not specifically disclosed the structure or fragment in the in the second domain of the fragment or variant thereof of at least 80% sequence identity of SEQ ID NO: 66 that must be retained to posses the abilities to (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide

into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. Therefore Applicants response as set forth supra is unpersuasive.

With regard to Point (E), consequently, the number of species disclosed by the specification is not representative of the genus of fragments/variants in (II) or (III) aforementioned above encompassed by the claimed genus. Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Even though the specification discloses the preparation of the variant single- chain polypeptides shown in SEQ ID NOs: 2, 4, 10, 12, and 26 (see Example 1, pages 62-68) and SEQ ID NOs: 20, 22, and 24 (Example, 2, pages 68-69) comprising multiple amino acid substitutions and/or insertions/extensions as compared with the amino acid sequence of the corresponding clostridial neurotoxin light chain and heavy chain HN and relative activities of single chain polypeptides, Applicants have not demonstrated or identified regions which need to be conserved in at least 80% sequence identity to SEQ ID NO: 66, hence the fragments/variants of the genus aforementioned above are not deemed persuasive. For example, given a single substitution mutant of SEQ ID NO: 66, there are 175 possible single amino acid (20% of SEQ ID NO:66). Hence there are $6 \times 10^{223}$ single substitution mutants. Given the instant claims encompass multiple substitution mutants, deletion mutants and insertional mutants the total number of variants encompassed by the instant claims is incalculable. Obviously the instant claims encompass more than single substitution mutants. Therefore the preparation of the variant single-chain polypeptides show in Example 1, pages 62-68 and Example, 2, pages 68-69 comprising multiple amino acid substitutions and/or insertions/extensions is not deemed persuasive. Consequently, the specification does not teach any structural limitations and the specification is silent to the correlation of its recited function. Therefore, since the specification fails to

adequately describe at least a substantial number of members of the genus as set forth supra to which the claims are based.

With regard to Point (F), the Capon and Invitrogen decisions are based on what is already known in the art therefore representative members of the genus was not necessary to disclose. However, SEQ ID NO: 66 is not well known in the art. Furthermore, the core structure of SEQ ID NO: 66 is not well known in the art, therefore one skilled in the art would not know the functions of any fragments or variants associated with the domains of the heavy and light chain domains of clostridial neurotoxins. Applicants have not specifically disclosed in the specification the structure of a fragment or variant of at least 80% sequence identity of the single chain polypeptide of SEQ ID NO: 66 that encompasses said first and second domains set forth supra capable of the recited functions. Moreover, Applicants have not described the genus of a single chain polypeptide in (II) and or (III) aforementioned above as claimed. Furthermore the example in the specification and Exhibits (A-D) filed 2/1/2010 are not representative of the claimed invention nor the genus of representative members claimed invention. Therefore Applicants response on the basis of Capon and Invitrogen decision aforementioned above is unpersuasive because the SEQ ID NO: 66 was not known in the art and the lack of written description in the specification and exhibits. Therefore the rejection has been maintained.

As outlined previously, to fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the isolated single chain polypeptide Applicant must describe the genus of a single chain polypeptide comprising a fragment/variant of at least sequence identity of the single chain polypeptide SEQ ID NO: 66, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native

clostridial neurotoxin binds. Applicant must adequately describe comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or fragment thereof capable of cleaving one or more vesicle or plasma membranes, wherein said second domain is a clostridial neurotoxin heavy chain or fragment thereof capable of translocating the polypeptide in the cell and increasing the solubility of the polypeptide.

The specification states, "a variant is an L-chain (or fragment thereof) in which one or more amino acid residues has been altered vis-a-vis a native clostridial L-chain sequence" (see pg. 4 last paragraph). The specification further states in one embodiment, the modification may involve one or more conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial L-chain sequence (see p. 4; see also pp. 12-13). However, any such fragment or variant must retain the aforementioned cleavage function." (see p. 4; see also pp. 12-13). The specification states, "a variant is an HN portion (or fragment thereof) in which one or more amino acid residues has been altered vis-a-vis a native clostridial HN domain sequence. In one embodiment, the modification may involve one or more conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial HN sequence. However, any such fragment or variant must retain the aforementioned (i) translocation and/or (ii) improved solubility function." (pp. 6-7; see also p. 13).

The specification discloses $LH_N/A$ incorporating an enterokinase protease activation site at the LC-$H_N$ junction and a C-terminal $(Glu)_8$ peptide (see pg. 44). The specification discloses SEQ ID NO: 24 a botulinum $H_N$ polypeptide fragment having only 107 residues sufficient to maintain solubility of a single chain polypeptide known as ($LH_{107}$/B, SEQ ID NO: 24) (see Example 2) which does not suggests that the specification discloses a core structure of the instant claims because the claimed invention is drawn to SEQ ID NO: 66. Furthermore, the core structure is not well known in the art, therefore one skilled in the art would not know the functions of any fragments or variants associated with the domains of the heavy and light chain domains of clostridial neurotoxins. Therefore the descriptions of fragments and variants of clostridial neurotoxins in the specification that Applicants stated in their response aforementioned above are merely representative of the claimed invention. Consequently, the

specification is only limited to (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. **Therefore SEQ ID NO: 66 meets the written description requirement not fragment or any variants of the claimed invention.**

Applicants have not disclosed in the specification any such fragment or variant of SEQ ID NO: 66 that must retain the "cleavage", translocation, and/or improved solubility function. The specification discloses $LH_N$/A incorporating an enterokinase protease activation site at the LC-$H_N$ junction and a C-terminal $(Glu)_8$ peptide (see pg. 44). Applicants have not disclosed in the specification any such fragment or variant of at least 80% sequence identity to SEQ ID NO: 66 that must retain the "cleavage", translocation, and/or improved solubility function. Moreover, Applicant has not specifically demonstrated in of at least 80% SEQ ID NO: 66 which C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ conveys the ability of thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds is indicated as not functional. Applicant has not specifically disclosed the structure of a fragment or variant of at least 80% sequence identity to the single chain polypeptide of SEQ ID NO: 66 that encompasses said first and second domains set forth supra capable of the recited functions. Applicants has not specifically disclosed the structure or fragment in the first domain of the fragment or variant thereof of at least 80% sequence identity to SEQ ID NO: 66 that must be retained to posses the abilities to cleave one or more vesicle or plasma membrane associated proteins essential to exocytosis, and the structure or fragment in the second domain the fragment or variant thereof of at least 80% sequence identity to SEQ ID NO: 66 that must be retained to posses the abilities to (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional

C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

Consequently, the number of species disclosed by the specification is not representative of the genus of fragments/variants in (II) or (III) aforementioned above encompassed by the claimed genus. Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. For example, given a single substitution mutant of SEQ ID NO: 66, there are 175 possible single amino acid (20% of SEQ ID NO:66). Hence there are $6 \times 10^{223}$ single substitution mutants. Given the instant claims encompass multiple substitution mutants, deletion mutants and insertional mutants the total number of variants encompassed by the instant claims is incalculable. Obviously the instant claims encompass more than single substitution mutants. Therefore the fragments/variants in the specification provided in the written description are insufficient to support the genus encompassed by the claim. The specification does not provide a core structure of SEQ ID NO: 66, therefore one skilled in the art would not know the core structure of SEQ ID NO: 66 because SEQ ID NO: 66 are not well known in the art. Consequently one skilled in the art would not know the functions of any fragments or variants associated with the domains of the heavy and light chain domains of clostridial neurotoxins. The specification does not teach any structural limitations and the specification is silent to the correlation of its recited function. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus as set forth supra to which the claims are based.

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of a single chain polypeptide, to which the claims are drawn, such as a correlation between the structure of an isolated single chain polypeptide structure comprising fragments or variants of the domains, and its functions, the capability of cleaving vesicle or plasma membranes (clostridial neurotoxin light chain) and also translocating the polypeptide in the cell and increasing the solubility of the polypeptide (clostridial neurotoxin heavy chain), so that the skilled artisan could immediately envision, or

recognize at least a substantial number of members of the claimed genus aforementioned above. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the amino acid or which amino acids might be replaced so that the resultant amino acid retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant amino acid retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus aforementioned above to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of a single chain polypeptide comprising fragments or variants of the domains capability of cleaving vesicle or plasma membranes (clostridial neurotoxin light chain in at least 80% sequence identity of SEQ ID NO: 66) capable of translocating the polypeptide in the cell and increasing the solubility of the polypeptide (clostridial neurotoxin heavy chain in at least 80% sequence identity of SEQ ID NO: 66).

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

*The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement* (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant/aforementioned above, an adequate written description of the claimed invention must

include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306).

Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of an isolated single chain polypeptide of the fragments or variant of at least 80% sequence identity to SEQ ID NO: 66, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds, further

comprising domains comprising clostridial neurotoxin heavy and light chain or fragments thereof, the skilled artisan could not immediately recognize or distinguish members of the claimed genus aforementioned above with capability of the first domain as a clostridial neurotoxin light chain or fragment thereof capable of cleaving one or more vesicle or plasma membranes and the second domain as a clostridial neurotoxin heavy chain or fragment thereof capable of translocating the polypeptide in the cell and increasing the solubility of the polypeptide.

Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of the single chain polypeptide of at least 80% sequence identity of SEQ ID NO: 66 as claimed possess the capabilities of the first domain as a clostridial neurotoxin light chain or fragment thereof that convey the capability of cleaving one or more vesicle or plasma membranes and the second domain as a clostridial neurotoxin heavy chain or fragment thereof capable of translocating the polypeptide in the cell and increasing the solubility of the polypeptide is not deemed representative of the genus of the single chain polypeptide of at least 80% sequence identity of SEQ ID NO: 66 and the first and second domains in the fragment/variant of as at least 80% sequence identity of SEQ ID NO: 66 as claimed to which the claims refer and therefore the claimed invention is not properly disclosed.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

***Enablement***

7. The rejection of claims 1-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for the reasons set forth in the previous office action. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph (enablement) on February 1, 2010 is carefully considered, but not found to be persuasive for the reasons below.

**Applicants Argues:**

A) In the Declaration of Clifford Charles Shone Under 37 CFR § 1.132 (attached herewith as Exhibit D), Dr. Shone discloses suitable tests for confirming clostridial neurotoxin light chain and clostridial neurotoxin heavy chain HN function. In Annex 1 of the Declaration, Dr. Shone states that a number of routine methods for confirming that a particular clostridial neurotoxin L-chain (or fragment or variant thereof) has the requisite protease activity were known prior to the filing date of the present application. Dr. Shone lists the SNAP-25 test as an example of a simple assay disclosed in the as- filed specification (page 5, lines 13-19) that was available prior to the filing date of the present application (Annex 1 of the Declaration). Dr. Shone also states that protease activity can be monitored by disappearance of the L-chain substrate or by detecting protease cleavage products using an assay comprising antibodies as described in PCT/GB95/01279 (Annex 1 of the Declaration). In Annex 2 of the Declaration, Dr. Shone states that a number of routine methods for confirming that a fragment or variant polypeptide has the required HN activity were known prior to the filing date of the present application. Dr. Shone states that the methods described by Blaustein, R.O., et al., FEBS 226:115-120 (1987) and Shone, C.C., et al, Eur. J. Biochem 167:175-180 (1987) are suitable (Annex 2 of the Declaration).

B) Therefore, a person of ordinary skill in the art would be familiar with simple, conventional tests for confirming whether a given polypeptide fragment or variant possesses the desired "first domain" function of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis. A person of ordinary skill in the would also be familiar with simple, conventional tests for confirming whether a given polypeptide fragment or variant possesses the desired "second domain" function of translocating the polypeptide into a cell and/or increasing the solubility of the polypeptide.

C) Furthermore, Applicants submit that for product or composition claims, teaching how to make and use a single embodiment is sufficient to meet the enablement requirement, even for broad claims covering many species. In Invitrogen Corp. v. Clontech Labs, Inc., 429 F.3d 1052

(Fed. Cir. 2005), the Federal Circuit, quoting the district court, stated that "[t]he enablement requirement is met if the description enables any mode of making and using the invention." 429 F.3d at 1071 (emphasis added). In Invitrogen, Clontech argued that the claims were not enabled because the specification allegedly failed to explain how to make the mutants using point mutations. See id. at 1070. The court rejected Clontech's argument, noting that the claims were not limited by the method of achieving the mutation. See id. at 1071. The court stated that "Invitrogen fully described an operable method for achieving the claimed invention." and held that the claims were not invalid for lack of an enabling disclosure. Id. Similarly, Applicants claim is directed to a product and is not limited by a method of using the product.

However, the art of record and the currently submitted evidence clearly establishes otherwise. Applicants submit that the specification provides considerable direction and guidance on how to practice the claimed invention and presents examples of variants and fragments of the single chain polypeptide. Furthermore, Applicants submit that the methods to determine whether the fragment or variant has the required activity were well-known to those of ordinary skill in the art. Therefore, Applicants submit that based on the as-filed specification and the assays available as of the filing date of the present application, one of ordinary skill in the art could make and use a single chain polypeptide or fragment or variant thereof, without undue experimentation.

**Examiner's Response to Applicants Arguments:**

With regard to Points (A), (B), and (C), the Declaration signed by Inventor Clifford Charles Shone is commensurate in scope but is deemed unpersuasive. The independent claim is drawn to an isolated polypeptide encompassing a single chain polypeptide comprising (I) SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (II) a fragment of the single chain polypeptide (I) that is at least 80% the length thereof; or III) a variant of the single chain polypeptide of (I) having at least 80% amino acid sequence homology therewith, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or fragment

thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis, and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a fragment thereof that (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

Applicants have not disclosed in the specification or in the declaration any such fragment or variant of at least 80% sequence identity to SEQ ID NO: 66 that must retain the "cleavage", translocation, and/or improved solubility function. Furthermore, the specification discloses $LH_N$/A incorporating an enterokinase protease activation site at the LC-$H_N$ junction and a C-terminal $(Glu)_8$ peptide (see pg. 44). The specification discloses SEQ ID NO: 24 a botulinum $H_N$ polypeptide fragment having only 107 residues sufficient to maintain solubility of a single chain polypeptide known as ($LH_{107}$/B, SEQ ID NO: 24) (see Example 2). Therefore, the specification is only limited to (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

However, the specification does not provide adequate description of the claimed genus of variants in (II) or (III) aforementioned above. Moreover, Applicant has not specifically demonstrated in of at least 80% SEQ ID NO: 66 which C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ conveys the ability of thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds is indicated as not functional. Applicant has not specifically disclosed the structure of a fragment or variant of at least 80% the length thereof the single chain

polypeptide of SEQ ID NO: 66 that encompasses said first and second domains set forth supra capable of the recited functions. Applicants has not specifically disclosed the structure or fragment in the first domain of the fragment or variant thereof of at least 80% SEQ ID NO: 66 that must be retained to posses the abilities to cleave one or more vesicle or plasma membrane associated proteins essential to exocytosis, and the structure or fragment in the second domain the fragment or variant thereof of at least 80% SEQ ID NO: 66 that must be retained to posses the abilities to (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. Therefore in regards to Applicants response the structure of clostridial neurotoxins and the function of their light chain and HN domains as being well-known at the time of filing is unpersuasive.

Applicants have not demonstrated or identified regions which need to be conserved in at least 80% sequence identity to SEQ ID NO: 66, hence the fragments/variants of the genus aforementioned above are not deemed persuasive. For example, given a single substitution mutant of SEQ ID NO: 66, there are 175 possible single amino acid (20% of SEQ ID NO:66). Hence there are $6 \times 10^{223}$ single substitution mutants. Given the instant claims encompass multiple substitution mutants, deletion mutants and insertional mutants the total number of variants encompassed by the instant claims is incalculable. Obviously the instant claims encompass more than single substitution mutants. Therefore, the creation and testing assays of all the mutants to determine whether a particular clostridial neurotoxin HN portion (or equivalent HN component) has requisite translocation function and activity constitutes an undue burden to one skilled in the art. Therefore the fragments/variants in the specification are insufficient to support the genus encompassed by the claim. Furthermore, because Applicants have not described the genus of single chain polypeptide in (II) and or (III) aforementioned above as claimed, the example in the specification and the Exhibits (A-D) filed 2/1/2010 are not representative of the claimed invention nor the genus of representative members claimed

invention. Therefore although Dr. Shone discloses in the Declaration suitable tests for confirming routine methods for confirming that a particular clostridial neurotoxin L-chain (or fragment or variant thereof) that has the requisite protease activity and clostridial neurotoxin light chain and clostridial neurotoxin heavy chain HN function is unpersuasive. Consequently, the specification does not teach any structural limitations and the specification is silent to the correlation of its recited function. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus as set forth supra to which the claims are based. Therefore Applicants responses aforementioned above are unpersuasive and the rejection is maintained.

As outlined previously, because the specification, while being enabling for a single chain polypeptide (first and second domain is clostridial neurotoxin light chain and clostridial neurotoxin heavy chain respectively), wherein single chain polypeptide comprising SEQ ID NO:66, does not reasonably provide enablement for a single chain polypeptide comprising at least 80% sequence identity to SEQ ID NO: 66 and the fragments of the domains of the Clostridial neurotoxin light chain or Clostridial neurotoxin heavy chain of at least 80% sequence identity to SEQ ID NO: 66. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is not enabled for any single chain polypeptide comprising fragments or variants thereof of the domains comprising clostridial neurotoxin light and heavy chains or the fragment or variants of at least 80% sequence identity to SEQ ID NO: 66. Furthermore, the specification does not reasonably enable any single chain polypeptide comprising fragments or variants thereof of the domains in at least 80% sequence identity to SEQ ID NO: 66 aforementioned above for cleavage (first domain), translocation into a cell, and/or increasing the solubility (second domain). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the

existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention:

The claims are drawn to an isolated polypeptide, wherein said isolated polypeptide is a single chain polypeptide selected from the group consisting of: (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (II) a fragment of the single chain polypeptide (I) that is at least 80% the length thereof, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or fragment thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis, and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a fragment thereof that (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said fragment of the single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the

polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; or (III) a variant of the single chain polypeptide of (I) having at least 80% amino acid sequence homology therewith, comprising first and second domains, wherein said first domain is a clostridial neurotoxin light chain or a variant thereof that cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis and wherein said second domain is a clostridial neurotoxin heavy chain $H_N$ or a variant thereof that (i) translocates the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said variant of the single chain polypeptide lacks a function C-terminal part of a clostridial neurotoxin heavy chain $H_C$, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

Breadth of the claims

The breadth of the claims is very broad and the quantity of experimentation required is undue. The claims encompass all fragments and variants of clostridial neurotoxin light chain, clostridial neurotoxin heavy chain portion or a fragment, and further fragments and variants of at least 80% sequence identity of SEQ ID NO: 66 which are overly broad. The claims encompass a myriad of possible combinations that would comprise the single chain polypeptide as claimed. Furthermore the claims encompass any type of modifications (substitution, insertion, deletion, etc.) and the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Guidance in the specification/Working Examples

The specification disclosed various construct variants (see pgs. 64-78). The specification states, "a variant is an L-chain (or fragment thereof) in which one or more amino acid residues has been altered vis-a-vis a native clostridial L-chain sequence" (see pg. 4 last paragraph). The specification further states in one embodiment, the modification may involve one or more

conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial L-chain sequence (see p. 4; see also pp. 12-13). However, any such fragment or variant must retain the aforementioned cleavage function." (see p. 4; see also pp. 12-13). The specification states, "a variant is an HN portion (or fragment thereof) in which one or more amino acid residues has been altered vis-a-vis a native clostridial HN domain sequence. In one embodiment, the modification may involve one or more conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial HN sequence. However, any such fragment or variant must retain the aforementioned (i) translocation and/or (ii) improved solubility function." (pp. 6-7; see also p. 13).

The specification is only limited to (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. However, Applicants have not disclosed in the specification any such fragment or variant of at least 80% sequence identity to SEQ ID NO: 66 that must retain the "cleavage", translocation, and/or improved solubility function. Applicants have not disclosed in the specification any such fragment or variant of at least 80% sequence identity of SEQ ID NO: 66 that must retain the "cleavage", translocation, and/or improved solubility function. The specification discloses $LH_N/A$ incorporating enterokinase protease activation site at the LC-$H_N$ junction and a C-terminal $(Glu)_8$ peptide (see pg. 44).

The specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants, if any, can be made which retain the biological activity of the intact protein. For example, given a single substitution mutant of SEQ ID NO: 66, there are 175 possible single amino acid (20% of SEQ ID NO:66). Hence there are $6 \times 10^{223}$ single substitution mutants. Given the instant claims encompass multiple substitution mutants, deletion mutants and insertional mutants the total

number of variants encompassed by the instant claims is incalculable. Obviously the instant claims encompass more than single substitution mutants. Therefore, the creation and testing of all the mutants constitutes an undue burden on one skilled in the art. Therefore the specification has not set forth any enablement with regard to the myriad possibilities of the fragments or variants in each of the first, second, nor the myriad possible combinations of these fragments or variants of each of these domains that would comprise the single chain polypeptide as claimed. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed domains, for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species, which could not be distinguished without undue experimentation. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions that would encompass the fragments and variants of the domains of the single chain polypeptide as presently claimed. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model.

State of the Art

It is known in the art that derivatives (i.e., fragments or variants), which are obtained by substitutions, deletions, or modifications of the amino acids of a protein alter the function of the protein. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's

sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Also as evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding.

In conclusion, the claimed inventions are not enabled for a single chain polypeptide comprising at least 80% sequence identity to SEQ ID NO: 66 and the fragments of the domains of the Clostridial neurotoxin light chain or Clostridial neurotoxin heavy chain of at least 80% sequence identity to SEQ ID NO: 66. The claims encompassing all fragments and variants of clostridial neurotoxin light chain, clostridial neurotoxin heavy chain, and further fragments and variants of SEQ ID NO: 66 is overly broad. Moreover, the specification discloses SEQ ID NO: 24 as a botulinum $H_N$ polypeptide fragment having only 107 residues sufficient to maintain solubility of a single chain polypeptide known as ($LH_{107}$/B, SEQ ID NO: 24) (see Example 2). Therefore, the specification is only limited to (I) a single chain polypeptide comprising SEQ ID NO: 66, wherein said single chain polypeptide comprises first and second domains, wherein said first domain is a clostridial neurotoxin light chain and said second domain is a clostridial neurotoxin heavy chain $H_N$, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. It is not routine in the art to screen for positions within the protein's sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility limited in any protein. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art. In view of the lack of support in

the art and specification, associated with regard to the single chain polypeptide as claimed and the changes which can be made in the single chain polypeptide structure to make it a fragment or variant of the domains and still maintain their function as claimed, it would require undue experimentation on the part of the skilled artisan to make and use the single chain polypeptide as claimed. Therefore the claims are not enabled.

***New Grounds of Rejections***

***35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 1-30 under 35 U.S.C. 102(b) as being anticipated by (Willems et al Res. Microbiol. (1993) Vol. 144 pgs. 547-556).

Willems et al disclose SEQ ID NO: 66 which encompasses a fragment of a single chain polypeptide of the claimed invention. Hence SEQ ID NO: 66 inherently have the characteristics of a fragment of the single chain polypeptide that is at least 80% the length thereof, comprising first and second domains and lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see STIC results). Consequently, because Willems et al anticipate the same fragment of the single chain polypeptide of the instant invention, Willems et al disclose all limitations in the dependent claims of the claimed invention and hence Willems et al must exhibit the same properties of the instant invention.

***New Grounds of Rejections***

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir.

1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-3, 5-15, and 17-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 11-23, 25-26 of copending US Patent No. 7,674,470.

A) In the instant case, the claims are drawn to an isolated polypeptide, wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_C$ thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein:- said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence (I) SEQ ID NO: 66; or (II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said variant lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated $H_c$, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (claim 1), wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain and tetanus neurotoxin heavy chain (claims 2-3), wherein said second domain is a clostridial toxin heavy chain Hc portion (claim 5), wherein said clostridial neurotoxin heavy chain is a

botulinum neurotoxin type A chain (claim 6), wherein the second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain (claim 7), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (claim 8), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain (claim 9), wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain (claim 10), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (claim 11), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (claim 12), comprising a site for cleavage by a proteolytic enzyme (claim 13), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 14), wherein the cleavage site allows proteolytic cleavage of the first and second domains (claim 15), a polypeptide obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide (claim 17), wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc (claim 18).

B) Claims 1-9, 11-23, 25-26 of US Patent No. **7,674,470** teach an antigenic composition comprising a single chain polypeptide comprising first and second domains, wherein: said first domain is a clostridial neurotoxin light chain or a variant thereof, or a fragment of said light chain or variant wherein said variant or fragment has a common antigenic cross reactivity to said clostridial neurotoxin light chain; and said second domain is a clostridial neurotoxin heavy chain HN portion or a variant, wherein said variant or fragment has a common antigenic cross reactivity to said clostridial neurotoxin heavy HN portion; and wherein said domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (second domain lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the

polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds) (see claim 1), wherein said clostridial neurotoxin light chain is a botulinum light chain/tetanus neurotoxin light chain (see claims 2-3), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin heavy chain and tetanus neurotoxin heavy chain (see claims 4-5), wherein said second domain is a clostridial toxin heavy chain HN portion (see claim 7), wherein the second domain lacks a C- terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 8), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A/type B chain (see claims 9 and 12),wherein the second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain (see claim 11), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain (see claim 13), wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain (see claim 14), wherein the clostridial neurotoxin light chain is a botulinum toxin type B light chain, and the second domain comprises the 417 N-terminal amino acids of a botulinum toxin type B heavy chain (claim 15), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a tetanus toxin chain (claim 16), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (see claim 17), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (see claim 18), wherein a polypeptide is lacking a portion designated Hc of a clostridial neurotoxin heavy chain (see claims 19-20), comprising a site for cleavage by a proteolytic enzyme (see claim 21), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 22), wherein the site for cleavage allows proteolytic cleavage of the first and second domains (claim 23), antigenic composition obtainable by a first nucleic acid sequence encoding said cleavage site within a second nucleic acid encoding a single chain polypeptide (see claim 25), wherein a single chain polypeptide (antigenic comprising a single chain polypeptide) is SEQ ID: 66 (see claim 26 and STIC results attachment).

Although the conflicting claims are not identical, they are not patentably distinct. The U.S. Patent No. 7,674,470 recites the "single chain polypeptide". The species of the "single chain

polypeptide" anticipate the genus claims of any "single chain polypeptide". Thus, claims 1-3, 5-15, and 17-18 encompassing the "the isolated polypeptide" in the present application are obvious over claims 1-9, 11-23, 25-26 of U.S. Patent No. 7,674,470.

***Conclusion***

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert A. Zeman/

for Nina Archie, Examiner of Art Unit 1645